

Derivatives of Heterocyclic Amines with
1,2-Epoxy-3-aryloxypropanes and Chlorocarbonates

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PREFACE

To facilitate handling the survey of the literature, the subject matter of this dissertation is presented in three sections. In the first section the syntheses of intermediates, 1,2-epoxy-3-aryloxypropanes, is presented. Amino alcohol derivatives formed by reacting these intermediates with pyrrolidine, piperidine, or morpholine are discussed in the second section. In the third section chloro-carbonate derivatives of pyrrolidine are discussed. The material is presented in detailed form so that future investigators may easily duplicate this work.

All temperatures refer to the centigrade scale, and its symbol is omitted. All melting points and boiling points reported are corrected values. The thermometers used were calibrated against a set of thermometers standardized by the Bureau of Standards.

The dichlorohydrin used in the preparation of the 1,2-epoxy-3-aryloxypropanes is a commercial mixture composed of approximately 70% 2,3-dichloro-1-propanol and 30% 1,3-dichloro-2-propanol obtained from Shell Chemical Corporation and used without further purification.

Yields of 1,2-epoxy-3-aryloxypropanes are based upon the molar quantity of phenol or substituted phenol which was used in the synthesis. In the case of the amino alcohol derivatives, the yields are based upon the amount of 1,2-epoxy-3-aryloxypropane used. The yields of the chloro-carbonate derivatives are based upon the amounts of pyrrolidine used.

In reporting the recrystallizing solvents there will appear mixtures as: ethanol-ether, absolute ethanol-acetone-ether, and ethanol-water. The first-mentioned solvent in each case is the one which dis-

solves the product and the other(s) promote crystallization.

Unless indicated on data sheet, all compounds reported are new.

The manner of listing references is the customary one used by journals of the American Chemical Society. The abbreviations of journals are those adopted as official by Chemical Abstracts.

TABLE OF CONTENTS

Chapter		Page
	PREFACE	11
I	INTRODUCTION	1
II	PREPARATION OF THE INTERMEDIATE 1,2-EPOXY-3-ARYLOXYPROPANES	4
	Review of Literature	4
	Experimental Work	6
	1,2-Epoxy-3-phenoxypropane	7
	1,2-Epoxy-3-(p-chlorophenoxy)propane	9
	1,2-Epoxy-3-(g-chlorophenoxy)propane	11
	1,2-Epoxy-3-(2,4-dichlorophenoxy)propane	13
	1,2-Epoxy-3-(g-toloxyl)propane	15
	1,2-Epoxy-3-(g-toloxyl)propane	17
	1,2-Epoxy-3-(a-naphthoxy)propane	19
III	PRODUCTS FROM THE REACTION OF 1,2-EPOXY-3-ARYLOXY- PROPANES WITH PYRROLIDINE, PIPERIDINE, OR MORPHOLINE	21
	Review of Literature	21
	Experimental Work	22
	1-Phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane	23
	1-Phenoxy-2-hydroxy-3-(1-piperidyl)propane	25
	1-Phenoxy-2-hydroxy-3-(4-morpholinyl)propane	27
	1-(p-Chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane	29
	1-(p-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane	31
	1-(p-Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane	33

TABLE OF CONTENTS (Continued)

Chapter	Page
1-(<i>g</i> -Chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane	35
1-(<i>g</i> -Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane	37
1-(<i>g</i> -Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane	39
1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane	41
1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane	43
1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane	45
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane	47
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(1-piperidyl)propane	49
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(4-morpholinyl)propane	51
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane	53
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(1-piperidyl)propane	55
1-(<i>g</i> -Toloxyl)-2-hydroxy-3-(4-morpholinyl)propane	57
1-(α -Naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane	59
1-(α -Naphthoxy)-2-hydroxy-3-(1-piperidyl)propane	61
1-(α -Naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane	63

TABLE OF CONTENTS (Continued)

Chapter	Page
IV	PRODUCTS FROM REACTION OF PYRROLIDINE AND CHLOROCARBONATES (METHYL THROUGH HEXYL) 65
	Review of Literature 65
	Experimental Work 66
	1-Carbomethoxypyrrolidine 68
	1-Carboethoxypyrrolidine 70
	1-Carbo- <u>n</u> -propoxypyrrolidine 72
	1-Carbo- <u>n</u> -butoxypyrrolidine 74
	1-Carbo- <u>iso</u> -butoxypyrrolidine 76
	1-Carbo- <u>n</u> -amoxypyrrolidine 78
	1-Carbo- <u>n</u> -hexoxypyrrolidine 80
	SUMMARY 82
	BIBLIOGRAPHY 83
	ACKNOWLEDGMENTS 86
	BIOGRAPHICAL ITEMS 87
	COMMITTEE REPORT

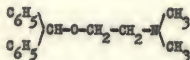
Chapter I

INTRODUCTION

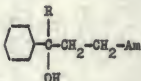
The search for new chemical compounds with high therapeutic value is wide-spread, especially in the field of the antihistaminics and antispasmodics. Much of this work has been directed towards the synthesis of amine alcohols and amine ethers and many variations have shown marked activity.

This dissertation describes the preparation of compounds which it was felt might have some physiological activity due to the types of groups which they possess. This investigation was limited to the synthesis of 1,2-epoxy-3-aryloxypropanes and their use as intermediates in the preparation of compounds which are both amine alcohols and amine ethers, the amine group being pyrrolidine, piperidine, or morpholine. There also appears a series of compounds prepared from pyrrolidine and chlorocarbonates (methyl through hexyl) which it was felt might show some therapeutic activity. Similar work on chlorocarbonates is underway at the present time in this laboratory.

The above-mentioned groups were decided upon after an examination of the literature had revealed that compounds in which they were present showed decided activity when tested clinically. Benadryl, a product of Parke, Davis and Company, is recognized as a standard in the field of antihistaminics and examination of its structure shows it to be an amine ether:



Borovicka and Vondracek (1) prepared derivatives of 1-benzhydryloxy-3-amino-2-propanol which have high antihistamine activity, where a methyl group was substituted in the benzhydryloxy group at the ortho, meta, and para positions and the amino group was piperidyl. Kolinsky and Protiva (2) prepared some basic ethers, which also show antihistamine activity, by substituting an aryl group for the benzhydryl group of Benadryl and a diethyl for the dimethyl amino group. One of the active constituents of the product Aspasan, diphenyl-1-piperidylpropane, prompted Ruddy and Buckley (3) to extend the work with variations of morpholinyl, dimethyl, and diethyl for the piperidyl group to determine if the spasmolytic activity would be increased. Antispasmodic activities are shown by compounds which are members of the two homologous series having the structure



in which R represents various hydrocarbon radicals and Am is morpholinyl or piperidyl. These homologous series were extended by Denton, et. al., (4) by variations in the aromatic ring. Yale, et. al., (5) and Mazurkiewicz and Supniewski (6) prepared a number of derivatives of 3-(p-toloxy)-1,2-propanediol, a product sold by E. R. Squibb & Sons as Tolserol, for pharmacological screening. Mazurkiewicz and Supniewski's compounds are nerve poisons, as is Tolserol, which is the most effective. Fournneau (7), (8) prepared some aryloxy-amino alcohols with marked antipyretic and analgetic properties. Geigy (9), (10) also reported therapeutically valuable aryloxy-amino alcohols but their use was not suggested.

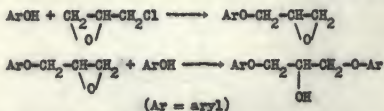
With this background, the work described in this dissertation was initiated.

Chapter II

PREPARATION OF THE INTERMEDIATE 1,2-EPOXY-3-ARYLOXYPROPANES

Review of Literature

One of the general methods which have been employed to prepare 1,2-epoxy-3-aryloxypropanes is the reaction of phenols with epichlorohydrin. Lindeman (11) prepared 1,2-epoxy-3-phenoxypropane, 1,2-epoxy-3-(*p*-toloxy)propane, and 1,2-epoxy-3-(α -naphthoxy)propane in 1891 by reacting epichlorohydrin with the corresponding phenol in a sealed tube heated to 150° for six hours. Others who also used epichlorohydrin are Boyd and Marle in 1908 (12), Marle in 1912 (13), Fournneau, et. al. in 1928 (14), Newman, et al. in 1947 (15), and Geigy in 1947 (16). Upon an overall inspection of this reaction, one could predict two products:



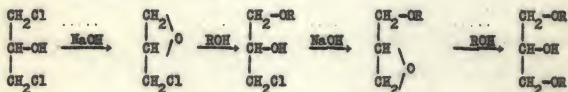
In some cases, (11), (12), and Boyd (17), both products have been isolated and reported.

Another general method for the preparation of 1,2-epoxy-3-aryloxypropanes is essentially a dehydrohalogenation reaction of a chlorohydrin with alkali. In 1913, Brenans (18) reported obtaining a mixture of 1,2-epoxy-3-(*g*-nitrophenoxy)propane and 1,3-(di-*g*-nitrophenoxy)-2-propanol by reacting *g*-nitrophenol with 1,3-dichloro-2-propanol in the presence of a 30% solution of sodium hydroxide for three weeks.

Rossing (19) in 1886 reported the formation of 1,3-diphenoxy-

2-propanol by the reaction of a solution of phenol and potassium hydroxide with the same dichlorohydrin, but apparently did not isolate the 1,2-epoxy-3-phenoxypropane. Glycerol diethers were also reported by Lindeman (11), Boyd (17), and Boyd and Marle (12) when they used epichlorohydrin.

Fairbourn, et. al. (20), (21) made a study of the reaction of sodium hydroxide upon alcoholic dichlorohydrin and found it to take place in four stages, which involve the formation and destruction of two ethylene-oxide rings consecutively as shown:



(R = methyl, ethyl, or phenyl)

Conditions which govern these four separate reactions have been investigated (21) and through modification it was found that each of the intermediate compounds could be isolated in good yield. The rings are produced by alkali, and are re-opened by further alkali or by acid, although they remain stable in neutral solution. From the published results of this general reaction, it is apparent that a substitution of phenols for alcohol does not change the mechanism, but strengthens it. It will be noted that there can be no difference in the product whether 1,2-dichloro-3-propanol or 1,3-dichloro-2-propanol is used.

Lefebvre, et. al. (22) and Levas and Lefebvre (23) investigated the possibility of using BF_3 in a benzene solution at 0° to catalyze the reaction of epichlorohydrin and phenol, but since the yield of 1,2-epoxy-

3-phenoxypropane which could be obtained from this method was much lower, it was not used for this work. Boyd and Marle (24) reported good results from using catalytic amounts of sodium hydroxide in the reaction of epichlorohydrin with phenol to form 1-chloro-3-phenoxy-2-propanol, from which 1,2-epoxy-3-phenoxypropane could be prepared by dehydrohalogenation using sodium hydroxide.

Another method for the preparation of the oxirane ring is the oxidation of olefins, which can not be classed as a general method, but is done in the laboratory by the use of oxidizing agents such as perbenzoic acid. Werner (25) prepared 1,2-epoxy-3-phenoxypropane by this method in 1948.

Experimental Work

The general method used for synthesis of the 1,2-epoxy-3-aryl-oxypropanes consisted of heating a mixture of the phenol and dichlorohydrin to 70° and adding a 27% solution of sodium hydroxide over a period of about 2 hours keeping the temperature between 70-80°. After heating the mixture for 15-60 minutes at 100°, it was then cooled, extracted with ether, dried, and distilled at reduced pressure.

All syntheses are described individually in the following pages, and each description is followed by a data sheet which tabulates some properties of the compound.

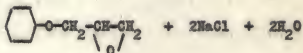
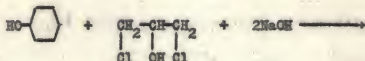
All of these intermediate compounds described have been made before. Only 1,2-epoxy-3-phenoxypropane had been made by the method herein described.

1,2-Epoxy-3-phenoxyp propane

In a two-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 188.2 g. (2 moles) of phenol and 258 g. (2 moles) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 160 g. (4 moles) of sodium hydroxide dissolved in 438 g. of water was added over a period of two hours and forty-five minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 100° and kept there for fifteen minutes. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-phenoxyp propane at 108-110° at 3 mm. The yield was 85.4 g. (or 28.5%).

1,2-Epoxy-3-phenoxypropane

Equation for Synthesis:



Molecular Formula	$\text{C}_9\text{H}_{10}\text{O}_2$
Molecular Weight	150.17
Boiling Point	108-110°/3 mm.
n_D^{25}	1.5278
Yield of Product, %	28.5

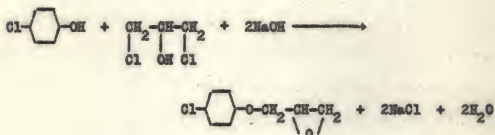
Note: This is not a new compound, (11), (12), (21), and was made by the method of Fairbourne, et. al., (21).

1,2-Epoxy-3-(p-chlorophenoxy)propane

In a one-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 128.56 g. (1 mole) of p-chlorophenol and 129 g. (1 mole) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 80 g. (2 moles) of sodium hydroxide dissolved in 219 g. of water was added over a period of one hour and fifty minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 100° and kept there for one hour. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(p-chlorophenoxy)propane at 95-97° at 0.8 mm. The yield was 58.4 g. (or 31.6%).

1,2-Epoxy-3-(p-chlorophenoxy)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_9\text{H}_9\text{ClO}_2$
Molecular Weight	184.62
Boiling Point	95-97°/0.8 mm.
n_D^{25}	1.5410
Yield of Product, %	31.6

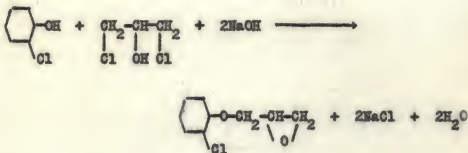
Note: This is not a new compound, but was made by a method different than reported in the literature (15), (16), (26).

1,2-Epoxy-3-(o-chlorophenoxy)propane

In a one-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 128.56 g. (1 mole) of *o*-chlorophenol and 129 g. (1 mole) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 80 g. (2 moles) of sodium hydroxide dissolved in 219 g. of water was added over a period of two hours and fifteen minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 100° and kept there for fifteen minutes. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(*o*-chlorophenoxy)propane at 90-95° at 1mm. The yield was 62.7 g. (or 34%).

1,2-Epoxy-3-(o-chlorophenoxy)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_9\text{H}_9\text{ClO}_2$
Molecular Weight.	184.62
Boiling Point	90-95°/1 mm.
n_D^{25}	1.5431
Yield of Product, %	34

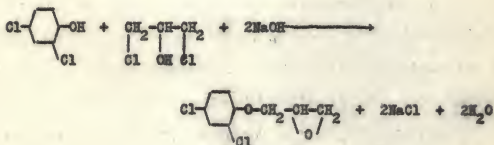
Note: This is not a new compound, but was made by a different method than that reported (26).

1,2-Epoxy-3-(2,4-dichlorophenoxy)propane

In a two-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 326.02 g. (2 moles) of 2,4-dichlorophenol and 258 g. (2 moles) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 160 g. (4 moles) of sodium hydroxide dissolved in 438 g. of water was added over a period of two hours and fifty minutes. Stirring was continued for an additional thirty minutes at the same temperature. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(2,4-dichlorophenoxy)propane at 121-124° at 1 mm. The yield was 100.3 g. (or 22.8%).

1,2-Epoxy-3-(2,4-dichlorophenoxy)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_9\text{H}_8\text{Cl}_2\text{O}_2$
Molecular Weight.	219.074
Boiling Point	121-124°/1 mm.
n_D^{25}	1.5571
Yield of Product, %	22.8

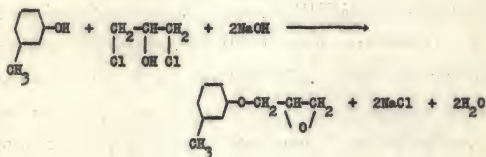
Note: This is not a new compound, but was made by a different method than that reported (15).

1,2-Epoxy-3-(*p*-toloxy)propane

In a two-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 216.26 g. (2 moles) of *p*-cresol and 258 g. (2 moles) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 160 g. (4 moles) of sodium hydroxide dissolved in 438 g. of water was added over a period of one hour and forty-five minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 103° and kept there for fifteen minutes. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(*p*-toloxy)propane at 85-88° at 0.8 mm. The yield was 139.6 g. (or 42.4%).

1,2-Epoxy-3-(p-toloxyl)propane

Equation for Synthesis:



Molecular Formula.	$\text{C}_{10}\text{H}_{12}\text{O}_2$
Molecular Weight	164.20
Boiling Point	85-88°/0.8 mm.
n_D^{25}	1.5239
Yield of Product, %	42.4

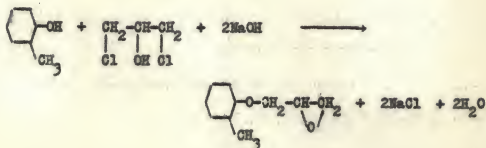
Note: This is not a new compound, but was made by a different method than that reported (13).

1,2-Epoxy-3-(o-toloxyl)propane

In a two-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 216.26 g. (2 moles) of o-cresol and 258 g. (2 moles) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 160 g. (4 moles) of sodium hydroxide dissolved in 438 g. of water was added over a period of one hour and forty-five minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 105° and kept there for twenty minutes. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate overnight. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(o-toloxyl)propane at 75-79° at 0.7 mm. The yield was 184 g. (or 56%).

1,2-Epoxy-3-(o-toloxyl)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_{10}\text{H}_{12}\text{O}_2$
Molecular Weight	164.20
Boiling Point	75-79°/0.7 mm.
n_{D}^{25}	1.5245
Yield of Product, %	56

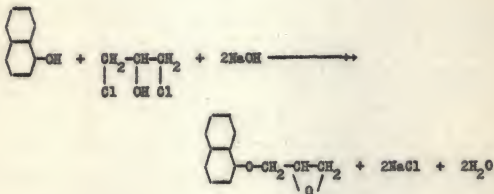
Note: This is not a new compound, but was made by a different method than that reported (27).

1,2-Epoxy-3-(α -naphthoxy)propane

In a two-liter, three-necked flask, provided with mechanical stirrer, addition funnel, and thermometer, were placed 288.32 g (2 moles) of α -naphthol and 258 g. (2 moles) of dichlorohydrin and the mixture was stirred thoroughly. Heating of the reaction mass was begun and the temperature was allowed to climb to 70°. While maintaining a temperature of 70-80°, a solution of 160 g. (4 moles) of sodium hydroxide dissolved in 438 g. of water was added over a period of one hour and thirty minutes. After the addition of the sodium hydroxide had been completed, the temperature was quickly increased to 90° and kept there for twenty minutes. The mixture was then cooled in an ice bath to room temperature and extracted with ether. The ether extract was dried over anhydrous sodium sulfate over-night. It was decanted before subjecting the mixture to distillation under water-pump vacuum to remove the low-boiling materials, collecting 1,2-epoxy-3-(α -naphthoxy)propane at 155-180° at 2 mm. The yield was 147.1 g. (or 36.8%).

1,2-Dioxy-3-(α -naphthoxy)propane

Equation for Synthesis:



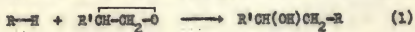
Molecular Formula	$C_{13}H_{12}O_2$
Molecular Weight	200.23
Boiling Point	155-180°/2 mm.
n_D^{25}	1.6110
Yield of Product, %	36.8

Note: This is not a new compound, but was made by a different method than that reported (11), (13), (14).

Chapter III

PRODUCTS FROM THE REACTION OF 1,2-EPOXY-3-ARYLOXYPROPANES WITH
PYRROLIDINE, PIPERIDINE, OR MORPHOLINEReview of Literature

The addition of compounds containing a labile hydrogen atom to an unsymmetrical 1,2-epoxide has long been a point of investigation. It can be illustrated by the following equations that the reaction may proceed in either of two directions giving two isomeric products:



$R-H$ represents any compound having a labile hydrogen atom. Krassousky (28) studied reactions of ammonia and of amines with unsymmetrical epoxides and reported that the reactions followed the first equation. The work of Boyd and Knowlton (27), Castro and Woller (29), Boyd (30), and Stephens (31) confirmed this observation.

Small amounts of water were observed by Krassousky (28) to be essential for the reaction of ammonia and 2-methyl-2,3-epoxybutane. Knorr (32) noted an increase in reactivity of ammonia and amines with ethylene oxide when a catalytic amount of water was present.

There are many variations in procedure for the addition of amines to unsymmetrical epoxides. Bradley and Stephenson (33) prepared numerous derivatives from 1,2-epoxy-3-aryloxypropanes and aliphatic amines by carrying out the reaction in the cold over a long period and with no mention of a catalyst. A diluent was used in some cases, but was not considered essential. Geigy (34) prepared 1-phenoxy-2-hydroxy-3-(4-morpholinyl)propane by heating a mixture of equal parts of

1-phenoxy-3-chloro-2-propanol and morpholine in xylene for six hours at 130-140°. Borovicka and Vondracek (1) prepared their compounds by heating the reactants to 100° in a sealed tube.

Experimental Work

The general method used for the synthesis of the amino alcohols consisted of heating the amine to reflux and adding the epoxide slowly. Heating of the mixture was continued for two hours after the addition of the epoxide was complete, and the mixture was subsequently distilled.

Catalytic amounts of water were used without any diluent.

All syntheses are described individually and each is followed by a data sheet upon which some properties of the compound are tabulated.

Two of the compounds, 1-phenoxy-2-hydroxy-3-(4-morpholinyl)propane and 1-(α -naphthoxy)-2-hydroxy-3-(1-piperidyl)propane, have been prepared previously by methods different from that described in this dissertation.

1-Phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane

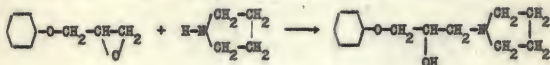
In a 100 ml. flask fitted with a reflux condenser were placed 15.6 g. (0.219 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 30 g. (0.2 mole) of 1,2-epoxy-3-phenoxypropane was added over a period of forty-five minutes. After the addition of 1,2-epoxy-3-phenoxypropane had been completed, the mixture was refluxed for two hours and fifteen minutes. At the end of this time the mixture was distilled and 1-phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 130-166° at 1 mm. The yield was 36.7 g. (or 83.2%).

The hydrochloride of 1-phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether. As soon as precipitation was complete, the product was filtered, recrystallized from a butanol-hexane mixture, and dried in a vacuum desiccator over calcium chloride. The melting point of the purified hydrochloride is 118.2-119.2°.

The hydrobromide of 1-phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane was prepared by passing anhydrous hydrogen bromide through a solution of the compound dissolved in anhydrous ether. The product was filtered as soon as precipitation was complete, was recrystallized from a butanol-hexane mixture, and dried in a vacuum desiccator over calcium chloride. The melting point of the purified hydrobromide is 116.2-118.2°.

1-Phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{13}H_{19}NO_2$
Molecular Weight	221.29
Boiling Point	130-166°/1 mm.
n_D^{25}	1.5335
Yield of Product, %	83.2
Soluble in.	Ethanol, Ether, Acetone
Insoluble in	Water

1-Phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane hydrochloride

Melting Point	118.2-119.2°
Recrystallising Solvent	Butanol-Hexane
Analysis: — Nitrogen, %	Calculated 5.43
	Found 5.31
— Chlorine, %	Calculated 13.76
	Found 13.70

1-Phenoxy-2-hydroxy-3-(1-pyrrolidyl)propane hydrobromide

Melting Point	116.2-118.2°
Recrystallising Solvent	Butanol-Hexane
Analysis: — Nitrogen, %	Calculated 4.63
	Found 4.56
— Bromine, %	Calculated 26.44
	Found 26.37

1-Phenoxy-2-hydroxy-3-(1-piperidyl)propane

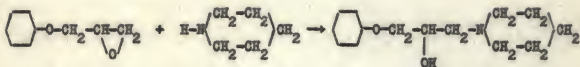
In a 100 ml. flask fitted with a reflux condenser were placed 14.07 g. (0.165 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 22.5 g. (0.15 mole) of 1,2-epoxy-3-phenoxypropane was added over a period of twenty minutes. After the addition of 1,2-epoxy-3-phenoxypropane had been completed, the mixture was refluxed for two hours, keeping the pot temperature below 150°. At the end of this time the mixture was distilled and 1-phenoxy-2-hydroxy-3-(1-piperidyl)propane was collected at 155-180° at 1 mm. The yield was 29.7 g. (or 84.4%).

The hydrochloride of 1-phenoxy-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether. As soon as precipitation was complete, the product was filtered, recrystallized from a butanol-hexane mixture, and dried in a vacuum desiccator over calcium chloride. The melting point of the purified hydrochloride is 150.9-151.9°.

The hydrobromide of 1-phenoxy-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen bromide through a solution of the compound dissolved in anhydrous ether. The product was filtered as soon as precipitation was complete, recrystallized from a butanol-hexane mixture, and dried in a vacuum desiccator over calcium chloride. The melting point of the purified hydrobromide is 134.1-135.1°.

1-Phenoxy-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:

Molecular Formula $\text{C}_{14}\text{H}_{21}\text{NO}_2$

Molecular Weight 235.32

Boiling Point 155-180°/1 mm.

 n_D^{25} 1.5292

Yield of Product, % 84.4

Soluble in Ethanol, Ether, and Acetone

Insoluble in Water

1-Phenoxy-2-hydroxy-3-(1-piperidyl)propane hydrochloride

Melting Point 150.9-151.9°

Recrystallizing Solvent Butanol-Hexane

Analysis:— Chlorine, % Calculated 13.04

Found 12.97

— Neutral Equivalent Calculated 271.79

Found 276.21

1-Phenoxy-2-hydroxy-3-(1-piperidyl)propane hydrobromide

Melting Point 134.1-135.1°

Recrystallizing Solvent Butanol-Hexane

Analysis:— Bromine, % Calculated 25.27

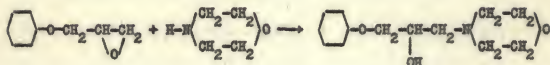
Found 25.03

1-Phenoxy-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.4 g. (0.165 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 22.5 g. (0.15 mole) of 1,2-epoxy-3-phenoxypropane was added over a period of forty-five minutes. After the addition of 1,2-epoxy-3-phenoxypropane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 150°. At the end of this time the mixture was distilled through a Vigreux column and two fractions of 1-phenoxy-2-hydroxy-3-(4-morpholinyl)propane were obtained. Fraction I came over at 150-170° at 1 mm. and had an index of refraction of 1.5338. The yield was 12.4 g. (or 34.9%). Fraction II came over at 170-184° at 1 mm. and had an index of refraction of 1.5336. The yield was 21 g. (or 59.2%). Both fractions solidified upon standing and were recrystallized from an ethanol-water mixture and dried in a vacuum oven, giving fine white crystals which melt at 67.5-68°. The yield was 94.1%.

1-Phenoxy-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



Molecular Formula	C ₁₃ H ₁₉ NO ₃
Molecular Weight	237.29
Boiling Point	150-184°/1 mm.
Melting Point	67.5-68°
n _D ²⁵	1.5336
Yield of Product, %	94.1
Soluble in	Ethanol, Acetone, Ether, and Dioxane
Insoluble in	Water
Recrystallising Solvent	Ethanol-Water
Analysis: — Nitrogen, %	Calculated 5.90
	Found 5.97

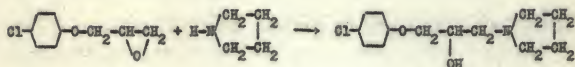
Note: This is not a new compound, but was made by a different method than that reported in the literature (34).

1-(p-Chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.74 g. (0.165 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 27.7 g. (0.15 mole) of 1,2-epoxy-3-(p-chlorophenoxy)propane was added over a period of forty minutes. After the addition of 1,2-epoxy-3-(p-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours. When the mixture cooled, the reaction mass turned to a solid which then was recrystallized from ethanol and dried in a vacuum desiccator. The crude yield was quantitative. The product, 1-(p-chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane, melts at 90-91°.

1-(p-Chlorophenoxy)-2-hydroxy-1-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_{13}\text{H}_{18}\text{ClNO}_2$
Molecular Weight	255.74
Melting Point	90-91°
Yield of Crude Product	Quantitative
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Ethanol
Analysis: — Nitrogen, %	
Calculated	5.48
Found	5.46
-- Neutral Equivalent	
Calculated	255.74
Found	256.14

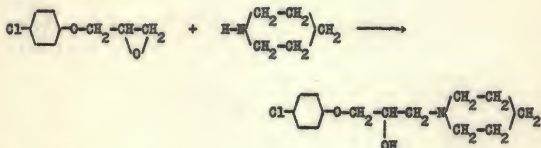
1-(p-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.07 g. (0.165 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 27.7 g. (0.15 mole) of 1,2-epoxy-3-(p-chlorophenoxy)propane was added over a period of twenty minutes. After the addition of 1,2-epoxy-3-(p-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours. A quantitative crude yield of the product solidified upon cooling and was recrystallized from ethanol. The product, 1-(p-chlorophenoxy)-2-hydroxy-3-(1-piperidyl)-propane, which was dried in a vacuum desiccator, melts at 74.6-75.1°.

The hydrochloride of 1-(p-chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the solution was slightly acidic. The product, which was filtered, washed with ether, and dried in a vacuum desiccator, melts at 157-158°.

1-(p-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_{14}\text{H}_{20}\text{ClNO}_2$
Molecular Weight	269.77
Melting Point	74.6-75.1°
Yield of Crude Product	Quantitative
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Ethanol
Analysis: — Neutral Equivalent	Calculated 269.77
	Found 266.04

1-(p-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

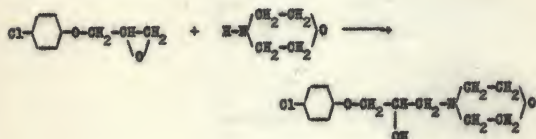
Melting Point	157-158°
Analysis: — Ionisable Chlorine, %	Calculated 11.58
	Found 11.51

1-(p-Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 7.54 g. (0.0865 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 14.5 g. (0.0785 mole) of 1,2-epoxy-3-(p-chlorophenoxy)propane was added over a period of fifteen minutes. After the addition of 1,2-epoxy-3-(p-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours and thirty minutes. The mixture was solid after cooling. Recrystallization from ethanol-water gave 1-(p-chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane which melts at 65.5-66.5°. The crude yield was quantitative.

1-(p-Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



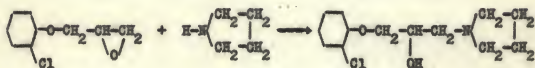
Molecular Formula	$\text{C}_{13}\text{H}_{18}\text{ClNO}_3$
Molecular Weight	271.74
Melting Point	65.5-66.5°
Yield of Crude Product	Quantitative
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Ethanol-Water
Analysis: -- Nitrogen, %	
Calculated	5.16
Found	5.07
-- Neutral Equivalent	
Calculated	271.74
Found	275.18

1-(*o*-Chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.7 g. (0.165 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 27.7 g. (0.15 mole) of 1,2-epoxy-3-(*o*-chlorophenoxy)propane was added during a period of thirty-five minutes. After the addition of 1,2-epoxy-3-(*o*-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours. At the end of this time the mixture was distilled through a Vigreux column and 1-(*o*-chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 144-145° at 0.7 mm. The yield was 30.1 g. (or 79%). The product solidified upon standing and was recrystallized from methanol-water. The purified product melts at 61-62°.

1-(o-Chlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_{13}\text{H}_{18}\text{ClNO}_2$
Molecular Weight	255.74
Boiling Point	144-145°/0.7 mm.
n_D^{25}	1.5440
Melting Point	61-62°
Yield of Product, %	79
Soluble in	Methanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Methanol-Water
Analysis: -- Nitrogen, %	
Calculated	5.48
Found	5.34
-- Neutral Equivalent	
Calculated	255.74
Found	254.25

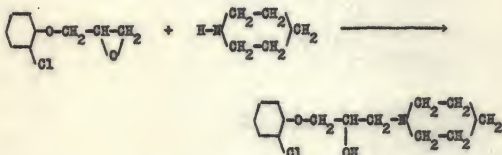
1-(*p*-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.07 g. (0.165 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 27.7 g. (0.15 mole) of 1,2-epoxy-3-(*p*-chlorophenoxy)propane was added over a period of thirty-five minutes. After the addition of 1,2-epoxy-3-(*p*-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 150°. At the end of this time the mixture was distilled through a Vigreux column and 1-(*p*-chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane was collected at 158-159° at 0.9 mm. The yield was 35 g. (or 87%). The product solidified upon standing and was recrystallized from hexane. The purified product melts at 70.1-71.1°.

The hydrochloride of 1-(*p*-chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether until a solid formed and the mixture was slightly acidic. The product was filtered and recrystallized from absolute ethanol-acetone-ether. The purified product melts at 151.4-152.4°.

1-(o-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{14}H_{20}ClNO_2$
Molecular Weight	269.77
Boiling Point	158-159°/0.9 mm.
Melting Point	70.1-71.1°
Yield of Product, %	87
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Hexane
Analysis: — Neutral Equivalent	Calculated 269.77
	Found 266.69

1-(o-Chlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

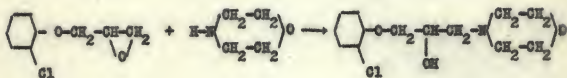
Melting Point	151.4-152.4°
Recrystallizing Solvent	Absolute ethanol-Acetone-Ether
Analysis: — Ionisable Chlorine, %	Calculated 11.58
	Found 11.39

1-(*o*-Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.45 g. (0.165 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 27.7 g. (0.15 mole) of 1,2-epoxy-3-(*o*-chlorophenoxy)propane was added during a period of forty minutes. After the addition of 1,2-epoxy-3-(*o*-chlorophenoxy)propane had been completed, the mixture was refluxed for two hours. At the end of this time the mixture was distilled through a Vigreux column and 1-(*o*-chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane was collected at 170-177° at 1 mm. The yield was 36 g. (or 88.2%). The product solidified upon cooling and was recrystallized from methanol-water. The purified product melts at 69-70°.

1-(o-Chlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



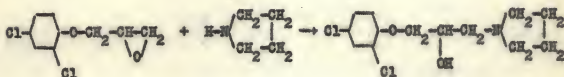
Molecular Formula		$C_{13}H_{18}ClNO_3$
Molecular Weight		271.74
Boiling Point		170-177°/1 mm.
n_D^{25}		1.5425
Melting Point		69-70°
Yield of Product, %		88.2
Soluble in	 Methanol, Ether, and Acetone	
Insoluble in	 Water	
Recrystallising Solvent	 Methanol-Water	
Analysis: — Nitrogen, %	Calculated	5.16
	Found	5.12
— Neutral Equivalent	Calculated	271.74
	Found	271.80

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 9.4 g. (0.132 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 26.3 g. (0.12 mole) of 1,2-epoxy-3-(2,4-dichlorophenoxy)propane was added during a period of thirty-two minutes. After the addition of 1,2-epoxy-3-(2,4-dichlorophenoxy)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 125°. At the end of this time, the mixture was distilled through a Vigreux column and 1-(2,4-dichlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 162-165° at 1 mm. The yield was 32.5 g. (or 93.3%). The product solidified upon standing and was recrystallized from an acetone-water mixture and dried in a vacuum desiccator over calcium chloride. The purified product melts at 79.1-79.6°.

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula		$\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_2$
Molecular Weight		290.198
Boiling Point		162-165°/1 mm.
Melting Point		79.1-79.6°
Yield of Product, %		93.3
Soluble in	 Ethanol, Ether, and Acetone	
Insoluble in	 Water	
Recrystallizing Solvent	 Acetone-Water	
Analysis: — Nitrogen, %	Calculated	4.83
	Found	5.02

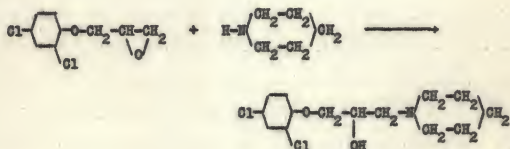
1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.2 g. (0.132 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 26.3 g. (0.12 mole) of 1,2-epoxy-3-(2,4-dichlorophenoxy)propane was added over a period of twenty-five minutes. After the addition of 1,2-epoxy-3-(2,4-dichlorophenoxy)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature below 138°. At the end of this time the mixture was distilled and 1-(2,4-dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane was collected at 168-170° at 1 mm. The yield was 32 g. (or 87.6%). The product solidified upon standing and was recrystallized from hexane. The purified product melts at 88-89°.

The hydrochloride of 1-(2,4-dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone. The product was filtered as soon as precipitation was complete, recrystallized from absolute ethanol-ether mixture, and dried in a vacuum desiccator over calcium chloride. The melting point of the purified hydrochloride is 149.9-150.9°.

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula		$\text{C}_{14}\text{H}_{19}\text{Cl}_2\text{NO}_2$
Molecular Weight		304.218
Boiling Point		168-170°/1 mm.
Melting Point		88-89°
Yield of Product, %		87.6
Soluble in	 Ethanol, Ether, and Acetone	
Insoluble in	 Water	
Recrystallising Solvent	 Hexane	
Analysis: — Neutral Equivalent	Calculated	304.218
	Found	299.810

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

Melting Point		149.9-150.9°
Recrystallising Solvent	 Absolute ethanol-Ether	
Analysis: — Ionisable Chlorine, %	Calculated	10.40
	Found	10.29

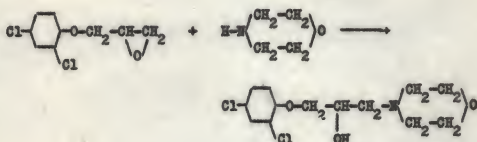
1-(2,4-dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.5 g. (0.132 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 26.3 g. (0.12 mole) of 1,2-epoxy-3-(2,4-dichlorophenoxy)propane was added during a period of thirty minutes. After the addition of 1,2-epoxy-3-(2,4-dichlorophenoxy)-propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature below 143°. At the end of this time the mixture was distilled and 1-(2,4-dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane was collected at 176-183° at 1 mm. The yield was 33.2 g. (or 90.5%).

The hydrochloride of 1-(2,4-dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether. The product was filtered as soon as precipitation was complete, recrystallized from an absolute ethanol-acetone mixture, and dried in a vacuum desiccator over calcium chloride. The pure product melts at 147.5-149° with some softening at 144.5°.

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



Molecular Formula	$\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_3$
Molecular Weight	306.19
Boiling Point	176-183°/1 mm.
Yield of Product, %	90.5
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water

1-(2,4-Dichlorophenoxy)-2-hydroxy-3-(4-morpholinyl)propane hydrochloride

Melting Point	147.5-149° *
Recrystallising Solvent	Absolute ethanol-Acetone
Analysis: — Nitrogen, %	Calculated 4.09
	Found 4.34
— Ionisable Chlorine, %	Calculated 10.35
	Found 10.28

* This product softens at 144.5°.

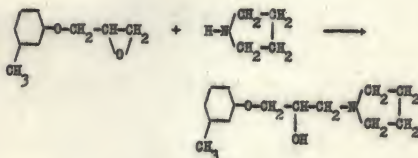
1-(*m*-Toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.72 g. (0.165 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(*m*-toloxyl)propane was added over a period of twenty minutes. After the addition of 1,2-epoxy-3-(*m*-toloxyl)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 140°. At the end of this time the mixture was distilled and 1-(*m*-toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 135-139° at 1 mm. The yield was 32.8 g. (or 92.8%).

The hydrochloride of 1-(*m*-toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether. The product was filtered as soon as precipitation was complete, recrystallized from an acetone-ether mixture, and dried in a vacuum desiccator over calcium chloride. The purified hydrochloride melts at 117.2-117.7°.

1-(p-Toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{14}H_{21}NO_2$
Molecular Weight	235.32
Boiling Point	135-139°/1 mm.
n_D^{25}	1.5300
Yield of Product, %	92.8
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water

1-(p-Toloxyl)-2-hydroxy-3-(1-pyrrolidyl)propane hydrochloride

Melting Point	117.2-117.7°
Recrystallising Solvent	Acetone-Ether
Analysis: — Nitrogen, %	
Calculated	5.15
Found	4.94
— Chlorine, %	
Calculated	13.05
Found	12.80

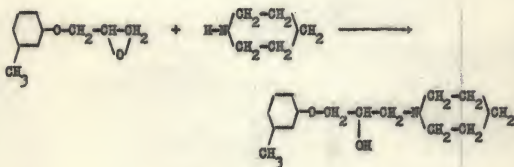
1-(*m*-Tolox)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.03 g. (0.165 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(*m*-tolox)propane was added over a period of twenty-five minutes. After the addition of 1,2-epoxy-3-(*m*-tolox)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 147°. At the end of this time the mixture was distilled and 1-(*m*-tolox)-2-hydroxy-3-(1-piperidyl)propane was collected at 132-136° at 1 mm. The yield was 34.3 g. (or 91.8%).

The hydrochloride of 1-(*m*-tolox)-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the mixture was slightly acidic. The product was filtered, recrystallised from acetone, dried in a vacuum desiccator over calcium chloride, and melts at 128.6-129.6°.

1-(p-Toloxv)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{15}H_{23}NO_2$
Molecular Weight	249.34
Boiling Point	132-136°/1 mm.
n_D^{25}	1.5259
Yield of Product, %	91.8
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water

1-(p-Toloxv)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

Melting Point	128.6-129.6°
Recrystallising Solvent	Acetone
Analysis: — Chlorine, %	Calculated 12.41
	Found 12.32

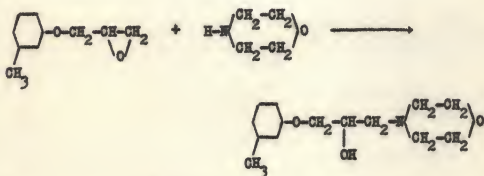
1-(η -Toloxyl)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.4 g. (0.165 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(η -toloxyl)propane was added over a period of twenty-three minutes. After the addition of 1,2-epoxy-3-(η -toloxyl)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 145°. At the end of this time the mixture was distilled and 1-(η -toloxyl)-2-hydroxy-3-(4-morpholinyl)propane was collected at 148-152° at 1 mm. The yield was 31.4 g. (or 83.3%).

The hydrochloride of 1-(η -toloxyl)-2-hydroxy-3-(4-morpholinyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in anhydrous ether. The product was filtered, recrystallized from an absolute ethanol-acetone-ether mixture, and dried in a vacuum desiccator over calcium chloride. The purified hydrochloride melts at 143.9-144.9°, with some softening at 137.9°.

1-(p-Toloxv)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



Molecular Formula		$C_{14}H_{21}NO_3$
Molecular Weight		251.318
Boiling Point		148-152°/1 mm.
Yield of Product, %		83.3
Soluble in		Ethanol, Ether, and Acetone
Insoluble in		Water

1-(p-Toloxv)-2-hydroxy-3-(4-morpholinyl)propane hydrochloride

Melting Point		143.9-144.9° *
Recrystallizing Solvent		Absolute ethanol-Acetone-Ether
Analysis: — Nitrogen, %	Calculated	 4.87
	Found	 5.04
— Chlorine, %	Calculated	 12.32
	Found	 12.32

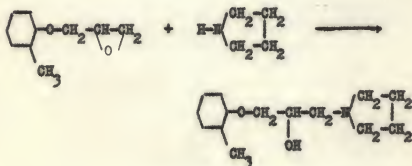
*This product softens at 137.9°.

1-(p-tolox)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 11.72 g. (0.165 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(p-tolox)propane was added over a period of twenty minutes. After the addition of 1,2-epoxy-3-(p-tolox)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 141°. At the end of this time the mixture was distilled and 1-(p-tolox)-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 124-128° at 1 mm. The yield was 31 g. (or 87.8%). The product solidified upon standing, was recrystallized from acetone, and dried in a vacuum desiccator over calcium chloride. The purified product melts at 48.7-50.2°.

1-(p-Toloxy)-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula		$C_{14}H_{21}NO_2$
Molecular Weight		235.32
Boiling Point		124-128°/1 mm.
Melting Point		48.7-50.2°
Yield of Product, %		87.8
Soluble in	 Ethanol, Ether, and Acetone	
Insoluble in	 Water	
Recrystallizing Solvent	 Acetone	
Analysis: -- Nitrogen, %	Calculated	5.95
	Found	5.69
-- Neutral Equivalent	Calculated	235.32
	Found	237.78

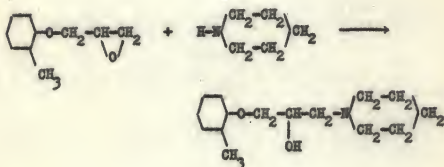
1-(*o*-Toloxyl)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.03 g. (0.165 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(*o*-toloxyl)propane was added over a period of thirty minutes. After the addition of 1,2-epoxy-3-(*o*-toloxyl)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 150°. At the end of this time the mixture was cooled and a quantitative crude yield was obtained. The residue was recrystallized from an acetone-water mixture and melts at 59-60°. The yield of the purified product was 30 g. (or 80.3%).

The hydrochloride of 1-(*o*-toloxyl)-2-hydroxy-3-(1-piperidyl)-propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the mixture was slightly acidic. The product was filtered, recrystallized from acetone, and dried in a vacuum desiccator over calcium chloride. The purified hydrochloride melts at 134.5-135.5°.

1-(o-Toloxv)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula	C ₁₅ H ₂₃ NO ₂
Molecular Weight	249.34
Melting Point	59-60°
Yield of Crude Product	Quantitative
Yield of Purified Product, %	80.3
Soluble in	Methanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Acetone-Water
Analysis: — Neutral Equivalent	Calculated
	Found
	249.34
	247.97

1-(o-Toloxv)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

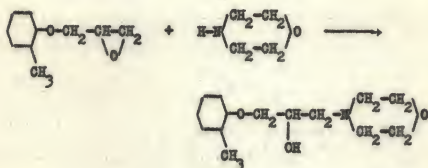
Melting Point	134.5-135.5°
Recrystallizing Solvent	Acetone
Analysis: — Chlorine, %	Calculated
	Found
	12.41
	12.29

1-(*o*-Telexy)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 14.4 g. (0.165 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 24.63 g. (0.15 mole) of 1,2-epoxy-3-(*g*-telexy)propane was added over a period of thirty minutes. After the addition of 1,2-epoxy-3-(*g*-telexy)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature under 150°. At the end of this time the mixture was distilled and 1-(*g*-telexy)-2-hydroxy-3-(4-morpholinyl)propane was collected at 139-141° at 1 mm. The yield was 34.1 g. (or 90.4%). The product solidified upon standing, was recrystallized from an acetone-water mixture, and dried in a vacuum desiccator over calcium chloride. The purified product melts at 66-67°.

1-(p-Toloxyl)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



Molecular Formula		$C_{14}H_{21}NO_3$
Molecular Weight		.251.32
Boiling Point		139-141°/1 mm.
Melting Point		66-67°
Yield of Product, %		90.4
Soluble in		Ethanol, Ether, and Acetone
Insoluble in		Water
Recrystallising Solvent		Acetone-Water
Analysis: — Nitrogen, %	Calculated	5.57
	Found	5.47
— Neutral Equivalent	Calculated	251.32
	Found	251.64

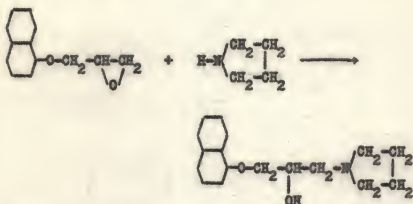
1-(α -Naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 7.81 g. (0.11 mole) of pyrrolidine and two drops of water, and the mixture was heated to reflux. Then 20.02 g. (0.1 mole) of 1,2-epoxy-3-(α -naphthoxy)propane was added over a period of ten minutes. After the addition of 1,2-epoxy-3-(α -naphthoxy)propane had been completed, the mixture was refluxed for two hours keeping the pot temperature below 150°. At the end of this time the mixture was distilled and 1-(α -naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane was collected at 178-186° at 0.5 mm. The yield was 20.7 g. (or 76.4%). The product solidified upon standing, was recrystallized from an ethanol-water mixture, and dried in a vacuum desiccator over calcium chloride. The purified product melts at 71.5-72.5°.

The hydrochloride of 1-(α -naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the mixture was slightly acidic. The product was filtered, recrystallized from an ethanol-acetone-ether mixture, dried in a vacuum desiccator over calcium chloride, and melts at 161.5-163°.

1-(α -Naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{17}H_{21}NO_2$
Molecular Weight	271.35
Boiling Point	178-186°/0.5 mm.
Melting Point	71.5-72.5°
Yield of Product, %	76.4
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Ethanol-Water

1-(α -Naphthoxy)-2-hydroxy-3-(1-pyrrolidyl)propane hydrochloride

Melting Point	161.5-163°
Recrystallizing Solvent	Ethanol-Acetone-Ether
Analysis: — Nitrogen, %	Calculated 4.55
	Found 4.24
Chlorine, %	Calculated 11.52
	Found 11.34

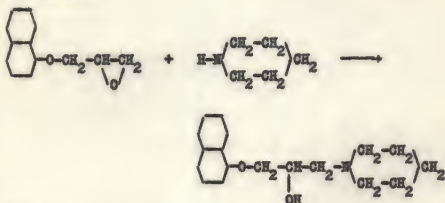
1-(α -Naphthoxy)-2-hydroxy-3-(1-piperidyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 9.37 g. (0.11 mole) of piperidine and two drops of water, and the mixture was heated to reflux. Then 20.02 g. (0.1 mole) of 1,2-epoxy-3-(α -naphthoxy)propane was added over a period of ten minutes. After the addition of 1,2-epoxy-3-(α -naphthoxy)propane had been completed, the mixture was refluxed for two hours keeping the pot temperature below 150°. At the end of this time the mixture was distilled and 1-(α -naphthoxy)-2-hydroxy-3-(1-piperidyl)propane was collected at 182-187° at 0.3 mm. The yield was 24 g. (or 84.2%). The product solidified upon standing, was recrystallized from an ethanol-water mixture, and dried over calcium chloride in a vacuum desiccator. The purified product melts at 82.1-83.1°.

The hydrochloride of 1-(α -naphthoxy)-2-hydroxy-3-(1-piperidyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the mixture was slightly acidic. The product was filtered, recrystallized from an absolute ethanol-acetone mixture, and dried in a vacuum desiccator over calcium chloride. It melts at 183.6-184.6° with some softening at 177.6°.

1-(α -Naphthoxy)-2-hydroxy-3-(1-piperidyl)propane

Equation for Synthesis:



Molecular Formula	$C_{18}H_{23}NO_2$
Molecular Weight	285.38
Boiling Point	182-187°/0.3 mm.
Melting Point	82.1-83.1°
Yield of Product, %	84.2
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water
Recrystallizing Solvent	Ethanol-Water

1-(α -Naphthoxy)-2-hydroxy-3-(1-piperidyl)propane hydrochloride

Melting Point	183.6-184.6° *
Recrystallizing Solvent	Absolute ethanol-Acetone
Analysis: — Chlorine, %	Calculated 11.02
	Found 10.89

* This product softens at 177.6°.

Note: This is not a new compound, but was made by a different method than that reported (14).

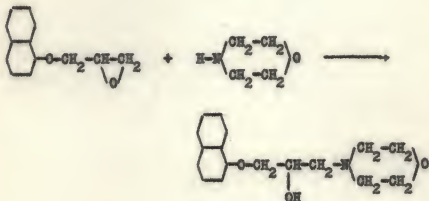
1-(α -Naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane

In a 100 ml. flask fitted with a reflux condenser were placed 9.58 g. (0.11 mole) of morpholine and two drops of water, and the mixture was heated to reflux. Then 20.02 g. (0.1 mole) of 1,2-epoxy-3-(α -naphthoxy)propane was added over a period of fifteen minutes. After the addition of 1,2-epoxy-3-(α -naphthoxy)propane had been completed, the mixture was refluxed for two hours, keeping the pot temperature below 150°. At the end of this time the mixture was distilled and 1-(α -naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane was collected at 190-206° at 0.5 mm. The yield was 24.8 g. (or 86.4%).

The hydrochloride of 1-(α -naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane was prepared by passing anhydrous hydrogen chloride through a solution of the compound dissolved in acetone until the mixture was slightly acidic. The product was filtered, recrystallized from an ethanol-acetone-ether mixture, and dried in a vacuum desiccator over calcium chloride. The purified hydrochloride melts at 190.1-191.1°.

1-(α -Naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane

Equation for Synthesis:



Molecular Formula	C ₁₇ H ₂₁ NO ₃
Molecular Weight	287.35
Boiling Point	190-206°/0.5 mm.
Yield of Product, %	86.4
Soluble in	Ethanol, Ether, and Acetone
Insoluble in	Water

1-(α -Naphthoxy)-2-hydroxy-3-(4-morpholinyl)propane hydrochloride

Melting Point	190.1-191.1°
Recrystallising Solvent	Ethanol-Acetone-Ether
Analysis: — Nitrogen, %	Calculated 4.33 Found 4.23
— Chlorine, %	Calculated 10.95 Found 10.82

Chapter IV

PRODUCTS FROM REACTION OF PYRROLIDINE AND CHLOROCARBONATES

(METHYL THROUGH HEXYL)

Review of Literature

A reaction of amines with chlorocarbonates can be generalized according to the following illustration:



where R-H represents any primary or secondary amine. This is a direct metathetical reaction splitting out hydrogen chloride which would form the salt of the amine if alkali were not added for its neutralization. However, the presence of too strong an alkali would decompose the chlorocarbonate.

Schotten (35), (36) prepared 1-carbomethoxypiperidine and 1-carbethoxypiperidine by slowly adding the alkyl chlorocarbonate to a solution of piperidine and potassium hydroxide and warming the mixture. Stevens and Watanabe (37) reported the preparation of N-carbopropoxy-DL-phenylalanine by treating DL-phenylalanine, dissolved in a sodium hydroxide solution and cooled in an ice bath, with milliliter portions of n-propyl chlorocarbonate. Sufficient amounts of sodium hydroxide were added simultaneously to keep the mixture alkaline during a reaction time of thirty minutes. Their method was essentially that of Carter et al. (38) and Bergmann and Zervas (39), the main difference being that they (38), (39) used toluene as a diluent for the chlorocarbonate.

Jilek (40) reported the preparation of 1-carbethoxymethyl-3-acetylpyridinium bromide from ethyl-α-bromoacetate and 3-acetylpyridine by heating the mixture on a steam bath for thirty minutes using benzene as a solvent. In the preparation of N-monocarbalkoxypiperazines, Moore et. al. (41) studied the addition of chlorocarbonates to piperazine and found that the pH should be adjusted between 2.8-4.6 in order to obtain the monosubstituted product. Jacobi (42) checked the work of Moore et. al. (41) and found optimum yields were obtained when the pH was 2.75. Pellard and Cole (43) prepared numerous monosubstituted piperazines as intermediates for their work and maintained the pH with a solution of sodium acetate as did the other investigators.

Pellard and Brown (44) prepared chlorocarbonate derivatives of N-monophenylpiperazine using a saturated solution of potassium carbonate instead of the stronger alkali and obtained high yields.

1-Carbethoxypyrrolidine was prepared by Signaigo and Adkins (45) by the reduction of 1-carbethoxypyrrole where the ring was reduced without changing the carbethoxy group.

Experimental Work

The general procedure followed in the preparation of these compounds was the addition of the chlorocarbonate to a solution of pyrrolidine in water, cooled to 10°. This addition was carried out over a period of 45-90 minutes and the temperature of the reaction was kept

below 15°. A saturated solution of potassium carbonate was added during the reaction to maintain alkaline conditions. The reaction mixture was then extracted with ether, dried over anhydrous potassium carbonate, and distilled.

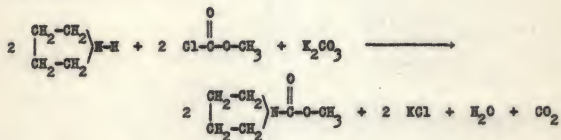
On the following pages all syntheses are described individually and each description is followed by a data sheet which tabulates some properties of the compound.

1-Carbomethoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 17.78 g. (0.25 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 25 g. (0.265 mole) of methyl chlorocarbonate was added over a period of forty-five minutes, keeping the temperature below 15°. The reaction was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of methyl chlorocarbonate had been completed, the mixture was stirred for two hours at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate for six hours. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbomethoxypyrrolidine was collected at 90-91° at 20 mm. The yield was 15 g. (or 46.6%).

1-Carbonethoxyoverrolidine

Equation for Synthesis:



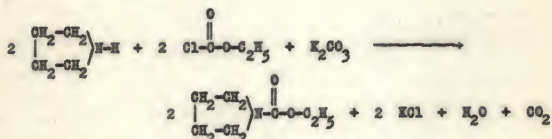
Molecular Formula	$\text{C}_6\text{H}_{11}\text{NO}_2$
Molecular Weight	129.16
Boiling Point	90-91°/20 mm.
n_D^{25}	1.4560
Yield of Product, %	46.6
Soluble in	Ethanol and Ether
Insoluble in	Water
Analysis: -- Nitrogen, %	
Calculated	10.84
Found	10.69

1-Carbethoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 23.7 g. (0.333 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 38 g. (0.35 mole) of ethyl chlorocarbonate was added over a period of one hour and thirty minutes keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of ethyl chlorocarbonate had been completed, the mixture was stirred for two hours at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate overnight. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbethoxypyrrolidine was collected at 98-99° at 20 mm. The yield was 37.5 g. (or 78.7%).

1-Carboethoxypyrrolidine

Equation for Synthesis:



Molecular Formula	$\text{C}_7\text{H}_{13}\text{NO}_2$
Molecular Weight	143.18
Boiling Point	98-99°/20 mm.
n_D^{25}	1.4523
Yield of Product, %	78.7
Soluble in	Ethanol and Ether
Insoluble in	Water
Analysis: — Nitrogen, %	
Calculated	9.78
Found	9.70

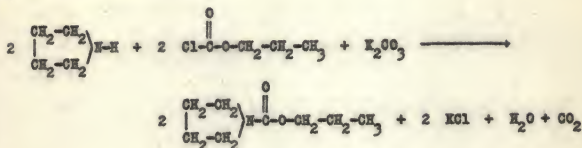
Note: This is not a new compound, but was made by the reduction of
1-carboethoxypyrrole (45).

1-Carbo- α -propoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 17.78 g. (0.25 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 32 g. (0.261 mole) of α -propyl chlorocarbonate was added over a period of one hour and fifteen minutes keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of α -propyl chlorocarbonate had been completed, the mixture was stirred for two hours at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate overnight. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbo- α -propoxypyrrolidine was collected at 109-110.5° at 20 mm. The yield was 32 g. (or 81.5%).

1-Carbo- α -cynoxycyrolidine

Equation for Synthesis:



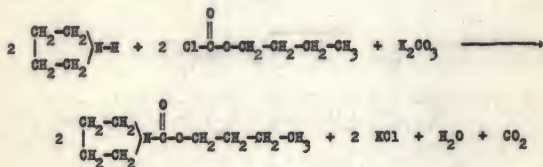
Molecular Formula	$\text{C}_8\text{H}_{15}\text{NO}_2$
Molecular Weight	157.21
Boiling Point	109-110.5°/20 mm.
n_D^{25}	1.4504
Yield of Product, %	81.5
Soluble in	Ethanol and Ether
Insoluble in	Water
Analysis: — Nitrogen, %	
Calculated	8.91
Found	8.80

1-Carbo- η -butoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 10.64 g. (0.15 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 22 g. (0.161 mole) of η -butyl chlorocarbonate was added over a period of one hour keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of η -butyl chlorocarbonate had been completed, the mixture was stirred for one hour at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate overnight. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbo- η -butoxypyrrolidine was collected at 126-128° at 20 mm. The yield was 13 g. (or (70%).

1-Carbo-n-butoxymorpholidine

Equation for Synthesis:



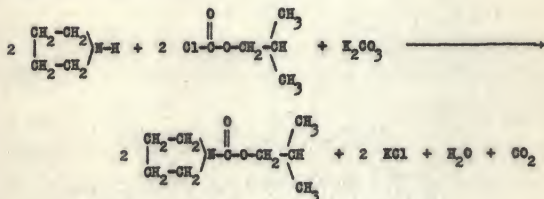
Molecular Formula		$\text{C}_9\text{H}_{17}\text{NO}_2$
Molecular Weight		171.24
Boiling Point		126-128°/20 mm.
n_D^{25}		1.4525
Yield of Product, %		70
Soluble in		Ethanol and Ether
Insoluble in		Water
Analysis: — Nitrogen, %	Calculated	8.18
	Found	8.04

1-Carbo-iso-butoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 10.64 g. (0.15 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 22 g. (0.161 mole) of iso-butyl chlorocarbonate was added over a period of forty-five minutes keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of iso-butyl chlorocarbonate had been completed, the mixture was stirred for one hour at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate several hours. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbo-iso-butoxypyrrolidine was collected at 121.5-122° at 20 mm. The yield was 18.6 g. (or 72.5%).

1-Carbo-iso-butoxy-pyrrolidine

Equation for Synthesis:



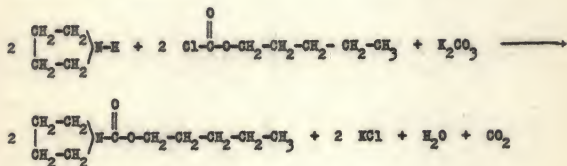
Molecular Formula	$\text{C}_9\text{H}_{17}\text{NO}_2$
Molecular Weight	171.24
Boiling Point	121.5-122°/ 20 mm.
n_D^{25}	1.4497
Yield of Product, %	72.5
Soluble in	Ethanol and Ether
Insoluble in	Water
Analysis: — Nitrogen, %	
Calculated	8.18
Found	7.98

1-Carbo- β -amoxypyrrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 10.64 g. (0.15 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 24 g. (0.159 mole) of β -amyl chlorocarbonate was added over a period of one hour, keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of β -amyl chlorocarbonate had been completed, the mixture was stirred for one hour at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate overnight. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbo- β -amoxypyrrrolidine was collected at 140-142° at 20 mm. The yield was 21.1 g. (or 76.3%).

1-Carbo- α -amerypyrrolidine

Equation for Synthesis:



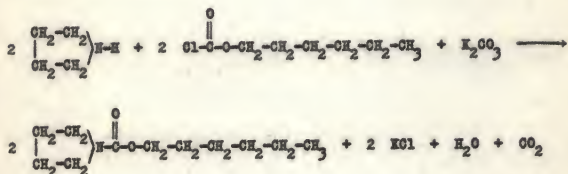
Molecular Formula		$\text{C}_{10}\text{H}_{19}\text{NO}_2$
Molecular Weight		185.27
Boiling Point		140-142°/20 mm.
n_D^{25}		1.4527
Yield of Product, %		76.3
Soluble in		Ethanol and Ether
Insoluble in		Water
Analysis: -- Nitrogen, %	Calculated	7.56
	Found	7.30

1-Carbo- η -hexoxypyrrolidine

In a 200 ml., three-necked flask, fitted with mechanical stirrer, thermometer, and dropping funnel, was placed 10.64 g. (0.15 mole) of pyrrolidine dissolved in 50 ml. of water. The mixture was cooled to 10° and 26 g. (0.158 mole) of η -hexyl chlorocarbonate was added over a period of one hour, keeping the temperature below 15°. The mixture was kept alkaline by the addition of a saturated solution of potassium carbonate. After the addition of η -hexyl chlorocarbonate had been completed, the mixture was stirred for one hour at room temperature. The reaction mixture was extracted with ether and the ether extract dried over anhydrous potassium carbonate for several hours. The solution was decanted and low-boiling materials were removed by use of water-pump vacuum. 1-Carbo- η -hexoxypyrrolidine was collected at 153.5-154° at 20 mm. The yield was 23.9 g. (or 80.2%).

1-Carbo-n-hexoxypyrrolidine

Equation for Synthesis:



Molecular Formula		$\text{C}_{11}\text{H}_{21}\text{NO}_2$
Molecular Weight		199.29
Boiling Point		153.5-154°/20 mm.
n_D^{25}		1.4522
Yield of Product, %		80.2
Soluble in		Ethanol and Ether
Insoluble in		Water
Analysis: — Nitrogen, %	Calculated	7.03
	Found	6.86

SUMMARY

A series of seven 1,2-epoxy-3-aryloxypropanes were prepared for use as intermediates in the production of compounds for pharmacological studies. The intermediates used are not new to the literature, but were prepared by a method different than those reported with the exception of 1,2-epoxy-3-phenoxypropane.

1,2-Epoxy-3-aryloxypropanes were reacted with three heterocyclic amines and nineteen compounds are reported which are new to the literature. Hydrogenchloride derivatives were made of thirteen of these compounds and their properties are recorded.

Seven chlorocarbonate derivatives of pyrrolidine have been prepared for pharmacological studies and are all new to the literature with the exception of 1-carbethoxypyrrolidine which had been reported obtained from a method different from that which was used in this investigation.

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BIOGRAPHICAL ITEMS

Raymond W. Ingvalson was born March 13, 1912, in Rockford, Illinois. He pursued his undergraduate studies at Carthage College, Carthage, Illinois, and was awarded the degree of Bachelor of Arts in Chemistry in June, 1935.

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COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Date February 2, 1952

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